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Pediatric Deep Brain Stimulation for Dystonia: Current State and Ethical Considerations

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Abstract

Dystonia is a movement disorder that can have a debilitating impact on motor functions and quality of life. There are 250,000 cases in the US, most with childhood onset. Due to the limited effectiveness and side effects of available treatments, pediatric deep brain stimulation (pDBS) has emerged as an intervention for refractory dystonia. However, there is limited clinical and neuroethics research in this area of clinical practice. This paper examines whether it is ethically justified to offer pDBS to children with refractory dystonia. Given the favorable risk-benefit profile, it is concluded that offering pDBS is ethically justified for certain etiologies of dystonia, but it is less clear for others. In addition, various ethical and policy concerns are discussed, which need to be addressed to optimize the practice of offering pDBS for dystonia. Strategies are proposed to help address these concerns as pDBS continues to expand.

Keywords

Dystonia; Deep brain stimulation; Pediatric; Neuroethics

Ryan's case

Ryan likes to play soccer, baseball, basketball, and football but he began running differently when he was eight years old. Once Ryan was diagnosed with inherited dystonia (i.e. dystonia 1 protein, DYT1), his mother described their situation as a "tornado." Ryan's dystonia first appeared in his left leg and soon spread across his body to his right arm and shoulder. Ryan started using a wheelchair, was very uncomfortable and unable to participate in activities he enjoyed. After trying multiple medications and therapies without meaningful benefit, the progression and severity of his condition led his doctor to consider pediatric deep brain stimulation (pDBS). After pDBS surgery and multiple programming visits, Ryan was markedly improved; he was able to perform daily life activities his dystonia previously interfered with, including walking, tying his shoes, and buttoning his shirts. Ryan's neurologists said: "Our goal will be to get him as good as we can, we don't promise

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perfection…but hopefully we get him to a point where he is stable and can do all the things he wants to do." Over time, Ryan's continued improvement allowed him to go back to school, and his mother expressed that Ryan and children like Ryan could still have a "bright future" due to the benefits pDBS could provide.[1]

Dystonia is a debilitating movement disorder that impacts patients' motor functions and quality of life.[2] Dystonia is characterized by involuntary muscle contractions that cause unwanted movements and postures. These movements and postures are repetitive and painful, and may present in a specific body part (i.e., focal dystonia) or across various body regions (i.e., generalized dystonia).[3] Patients with dystonia often have difficulty performing coordinated movements and may also experience an absence of motor outputs, which can be particularly disabling. Due to continued abnormal movements, patients may develop musculoskeletal deformities, which can lead to significant impairments in gait, standing, and hand function.[4]

Since 1999 pDBS for refractory dystonia has become increasingly common around the world, but there has been little systematic research (e.g., clinical trials) regarding its safety and effectiveness in minors.[5] Furthermore, there has been limited examination of the ethical challenges and implications of this practice.[6] We examine whether it is currently ethically justifiable to offer DBS for pediatric patients with refractory dystonia as well as the most ethically pressing considerations that need to be addressed.

Dystonia Treatment and Management:

There are two major types of dystonia. Inherited dystonia, commonly known as primary dystonia, is caused by mutations in single genes (e.g. *TOR1A*), which may or may not accompany degeneration or structural lesions.[7,8] Acquired dystonia, commonly known as secondary dystonia, generally develops out of neurological disease or injury (e.g., cerebral palsy). Dystonia may also be idiopathic and have no known cause.[9] The treatment and management of dystonia is challenging and often unsatisfactory.[10] Dystonia treatments include botulinum toxin (Botox) injections, various medications, and surgery.[11] Botox is frequently provided to patients with focal dystonia, but it less effective for generalized dystonia.[12] Pharmacological treatments are highly effective in a minority of dystonia patients (20–40%) and are particularly ineffective for patients with generalized dystonia.[13] High doses of medications are also needed to reach therapeutic benefit, which frequently lead to adverse effects. As a result, 61% of pediatric patients stop medications.[14] When Botox and medications are ineffective, surgical interventions are considered, such as intrathecal baclofen (ITB), which involves implanting a pump under the skin with a catheter that delivers medication into the spinal column. However, these treatments can still lack efficacy and cause complications in some patients.[15]

Pediatric Deep Brain Stimulation for Dystonia

pDBS has emerged as an intervention for refractory dystonia.[16] DBS involves surgically implanting electrodes in the brain that are connected via wires to a pacemaker-like battery-powered device placed in the chest or abdomen. Electrodes are implanted in one brain hemisphere (unilateral) or both (bilateral) to deliver stimulation to a specific brain target,

such as the globus pallidus interna (GPi), the most common target for dystonia, or the subthalamic nucleus (STN), to alter brain activity associated with dystonic movements.[17] Due to preliminary evidence that DBS for dystonia does not pose unreasonable risks and would likely be beneficial, pDBS for dystonia in the GPi or STN is offered under an FDA Humanitarian Device Exemption for children (≥ 7 years old) with refractory dystonia.[18,19]

Pediatric Refractory Dystonia

There is no clear estimate of pediatric refractory dystonia, but there are 250,000 dystonia cases in the U.S., and as described above, available treatments are often ineffective.[20] Inherited dystonia has an early onset occurring at 12 years of age on average and rarely develops after 29 years of age.[21,22] There are approximately 2–50 cases of inherited dystonia per million people under 20 years of age.[23] The prevalence for acquired dystonia is higher, but exact estimates are unknown due to inconsistent methodologies used across studies.[24] Both inherited and acquired dystonia are likely underreported due to misdiagnosis.[25]

If not effectively managed, dystonia can have significantly damaging effects on children's lives. Refractory symptoms of dystonia can be severe and potentially life threatening.[26,27] For example, uncontrolled muscular contractions can interfere with everyday purposeful movements. Children can also experience difficulty feeding, swallowing, breathing, and communicating.[28] Musculoskeletal deformity and fractures can develop over time, which profoundly affect movement, speech, vision and functionality.[29,30,31] Another symptom of dystonia that is frequently overlooked is pain, which may result from dystonic movements or musculoskeletal deformity.[32] Refractory symptoms can also have a significant and persistent impact on patients' lives (e.g., social isolation, low self-esteem, compounded psychopathology).[33,34,35] Dystonia patients commonly suffer from anxiety or obsessive-compulsive disorder, and depression is reported in 25% of dystonia patients.[36]

Early intervention, especially for severe, refractory cases, is particularly important for both clinical and psychosocial reasons.[37,38] Once formed, musculoskeletal deformities cannot be reversed by pDBS, and research suggests that adults and children who undergo DBS earlier after the onset of symptoms have better clinical outcomes.[39,40] In addition, the profound negative impact that refractory dystonia can have on patients' lives bolsters the argument for early intervention in severe, refractory cases.[41]

Clinical Benefits of pDBS:

Current evidence suggests that pDBS for severe, refractory dystonia is effective in improving both motor symptoms and quality of life, especially for inherited dystonia, like Ryan's case presented above.[42,43] A recent meta-analysis, which defined pediatric patients as ≤ 21 years old, analyzed the impact of DBS for different kinds of dystonia based on the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS).[44] This scale is one of the most common measures for dystonia, and includes a motor score and a disability score that reflect the severity and frequency of patients' dystonic movements.[45] The disability scale specifically assesses functions, such as speech, writing, feeding, eating, hygiene, dressing, and walking.[46]

Lior Elkaim and colleagues report that out of 111 patients with inherited dystonia (without degeneration or structural lesions), 88.2% showed at least a 20% improvement in motor scores.[47] A median improvement of 76.5% and 70% in motor and disability scores, respectively, was also observed in these patients (median follow-up 13.5 months). The meta-analysis further reports that in 72 patients with idiopathic dystonia, pDBS resulted in a median improvement of 50.5% and 39.2% in motor and disability scores, respectively (median follow-up 20 months).[48] However, the data are not as promising for other types of dystonia. In 50 cases with inherited dystonia (with degeneration or structural lesions), the median improvement in motor scores was 26.8% and zero improvement in disability scores (median follow-up 12 months). In 59 cases with acquired dystonia, the median improvement in motor and disability scores was only 11.1% and 3.5% (median follow-up 12 months).[49] Thus, the degree of symptom improvement after pDBS can vary significantly depending on the etiology of dystonia.

Non-Clinical Benefits of pDBS:

In addition to improvements in dystonia motor symptoms, pDBS has been shown to positively impact other meaningful aspects of patients' lives, including quality of life and perceived functional performance. Among 15 patients (adult and pediatric) with inherited and tardive acquired dystonia, quality of life improved in all patients with an overall improvement of 37% based upon the Parkinson's Disease Questionnaire-39 (PDQ-39).[50] This 39-item questionnaire assesses eight dimensions of quality of life, including mobility, activities of daily living, emotional well-being, stigma, social support, cognitions, communication, and bodily discomfort.[51] Long-term studies further support the positive effect DBS can have on quality of life. Takashi Tsuboi and colleagues measured health-related quality of life (HRQoL) using the short form health survey-36 (SF-36), which assesses various domains such as physical function, bodily pain, social function, and mental health. They demonstrated that HRQoL improvements persisted at a nine-year or later follow up in patients (adult and pediatric) who received DBS for inherited or idiopathic isolated dystonia.[52]

Additionally, Hortensia Gimeno and colleagues used the Canadian Occupational Performance Measure (COPM) to examine how pDBS affects pediatric patients' functional concerns. Patients were asked to rate the importance of their functional concerns, their perception of their performance, and their satisfaction with their performance based on a 1–10 scale.[53] Using this measure, functional performance and satisfaction improved in patients with both inherited and acquired dystonias one year after pDBS. The degree of improvement in perceived functional performance did not vary according to the severity or etiology of dystonia. Moreover, substantial improvements in functional performance and satisfaction were observed in pediatric patients with acquired dystonia even when their BFMDRS motor score did not significantly change, indicating that impairment scales do not always correlate with how patients perceive functional outcomes.[54]

As shown above, researchers use varying tools to measure what they are calling 'quality of life.' At minimum, greater transparency surrounding how quality of life is defined and measured is needed in the context of pediatric dystonia. Ideally, one comprehensive,

validated instrument should be used when assessing the impact of pDBS across different patient groups and clinics performing pDBS.

Risks of pDBS:

The motor and quality of life improvements must be considered in light of the potential risks of pDBS for dystonia.[55] The most common risks of pDBS for dystonia are: infection and hardware complications (e.g., lead fractures, lead failures, lead migration).[56,57] A prospective study of 129 pediatric patients found that infection occurred in 10.3% of patients.[58] Importantly, as many as 86% of patients who develop infections will require removal and reimplantation of the device.[59] On the other hand, generally no permanent sequelae occur as a result of infection.[60] This pediatric infection rate (10.3%) is twice the average infection rate found in some adult studies (5%).[61] However, adult infection rates can range from 1.2–15% and an infection rate of 7.4% was reported in dystonia patients of mixed ages according to another meta-analysis.[62,63] This higher infection rate of 10.3% is concerning and consistent with the higher pediatric complications rates observed for other implant procedures (e.g., ventriculoperitoneal shunting).[64] Among pediatric cases, infection rates were found to be lower in children under 7 years old (7.6%) and even lower if they had newer, Activa RC implants (4.7%).[65]

Hardware complications were reported in 18.4% of pediatric patients who received pDBS for dystonia, including electrode migration (2.3%), electrode/extension fracture (4.6%), electrode/extension malfunction (7.7%).[66] Another meta-analysis including 592 dystonia patients of mixed ages reported that the “highest rate of lead fracture or failure was found in dystonia patients (4.22%)” compared to Tourette syndrome (3.65%) and Parkinson’s Disease (0.41%).[67] This meta-analysis also reported that “[t]rauma, violent neck jerks, and spontaneous cause” were responsible for lead fractures or failures, but causes were “unreported or unknown for the vast majority of cases (89.31%).”[68] These hardware issues disrupt the connection between the pacemaker and electrodes, preventing the DBS system from delivering stimulation which may lead to the reemergence of symptoms. Lead fractures are not easily identified in 14.3–25% of suspected, open-circuit cases (i.e., high impedance and worsening of symptoms despite no radiological evidence of macroscopic fractures).[69] Different strategies can be used to manage these hardware issues, such as changing stimulation parameters, prolonged lead activation, and surgical revision, which comes with more risk. Few studies report improvement after such attempts are made, indicating that the management of hardware complications is still unclear.[70]

Infections and hardware complications such as lead fractures may lead to removal and reimplantation of the DBS leads. Removal and reimplantation involve risks associated with anesthesia and intracranial bleeding. One study that examined intracranial bleeding associated with removal of DBS leads reported that 10 out of 78 (12.8%) lead removals resulted in intracranial bleeding but the bleeding was not symptomatic.[71] Intracranial bleeding is more common during removal than during initial implantation (1%−3.4% per lead).[72] To our knowledge, no studies have reported the rate of brain bleeding during reimplantation of leads and how often these are symptomatic. Margaret Kaminska and

colleagues reported one case of intracranial bleeding out of 129 cases reviewed, and the bleeding was clinically silent.[73]

Deaths related to pDBS surgery are not common but possible. Across two pediatric dystonia meta-analyses and one dystonia meta-analysis of mixed ages, there were two reports of death: one due perioperative heart failure and the other due to an unknown cause (no post-mortem evidence of intracranial bleeding, but the death occurred 24 hours after electrode replacement).[74,75,76] Other rare (<2.5%) adverse events reported after pDBS for dystonia include low mood, difficulty recharging batteries, and skin erosion of the scalp leading to device removal.[77] Low-frequency stimulation for movement disorders may potentially minimize adverse effects and battery recharging/replacement.[78]

Weighing the Risks and Benefits:

The risks and benefits of pDBS cannot be clearly examined across all etiologies of dystonia due to the variability in outcomes for inherited, idiopathic, and acquired dystonia.[79] For inherited dystonia *without* degeneration or structural lesions, a considerable amount of evidence suggests that pDBS can provide substantial symptom improvement, particularly in children with inherited generalized dystonia and to a lower degree but still significant, children with idiopathic dystonia.[80,81] When weighing the risks and benefits of pDBS for inherited dystonia, the benefits appear to outweigh the potential risks because pDBS candidates suffer from severe forms of dystonia that are not responsive to medications and would continue to worsen, severely affecting their physical and psychosocial well-being. Furthermore, patients with inherited dystonia *without* degeneration or structural lesions consistently experience substantial, long-term improvement in motor symptoms, disability, and quality of life. On the other hand, the main risks associated with pDBS for inherited dystonia, such as infections and hardware malfunction, are significant, and can lead to additional surgical risks in some cases, but generally can be effectively managed without significant harm to patients' health.[82] This risk-benefit profile therefore suggests that it is ethically justified to offer pDBS to children with severe, refractory inherited dystonia *without* degeneration or structural lesions and idiopathic dystonia.

It is more challenging to take a decisive stance on the ethical permissibility of offering pDBS for acquired dystonia and inherited dystonia *with* degeneration or structural lesions. As discussed above, available data suggests that pDBS is less effective for these types of dystonia. Pediatric patients with inherited dystonia *with* degeneration or structural lesions show only a 26.8% improvement in motor symptoms and no improvement in disability, while pediatric patients with acquired dystonia (e.g., due to cerebral palsy) show only an 11.1% and 3.5% median improvement in motor symptoms and disability.[83] It is possible, however, that patients and caregivers might view a 26.8% or even 11% median improvement in motor symptoms as worth the risks of pDBS surgery because a seemingly marginal alleviation of symptoms could help minimize pain or facilitate caring for these children in meaningful ways.[84] More research examining patient and caregiver perspectives on risk-benefit assessments and quality of life outcomes are needed. This additional information would enhance stakeholders' ability to balance the risks and benefits of pDBS for these types of dystonia. Ideally, pDBS for acquired dystonia and inherited

dystonia *with* degeneration or structural lesions should take place within clinical trials to ensure more systematic data collection.

In the previous sections we discussed the challenges of refractory dystonia and examined the risks and benefits of pDBS for dystonia. Given current data, we conclude that offering pDBS is ethically justified for patients with some etiologies of dystonia, but for others it is less clear. There are, however, are a number of additional ethical and policy issues beyond risk-benefit assessment that need to be addressed to optimize the practice of offering pDBS for any type of dystonia. We outline several of these issues below: determinations of candidacy and the elimination of bias, access and cost barriers, managing expectations, identity formation, uncertainties and unknowns, the need for active registries, and the development of patient-centered decision support.

Determining Candidacy and Social Support Bias:

One major ethical challenge is determining candidacy for pDBS, which is a challenge relevant to all applications of DBS.[85] Research has shown that candidacy determinations for various medical interventions are often made using unjustified and unarticulated reasons.[86,87] Currently, "DBS treatment guidelines for pediatric patients with dystonia are not well-established" and there "is no recommendation about the severity of dystonia or any cut off scores for the same."[88,89] As a result, there is great potential for clinicians to interpret sweeping clinical statements, such as 'significant disability' and 'unresponsive to treatment' with variability across patients. This inconsistency in defining refractory dystonia is also reflected in eligibility criteria for DBS clinical trials. Some trials listed on clinicaltrials.gov simply state that eligible participants must be, "Diagnosed with nongeneralized cervical dystonia by a movement disorders neurologist," and must have "had adequate trials of medical therapy."[90] Another pediatric trial listed requires, "Dystonia symptoms that are sufficiently severe, in spite of best medical therapy, to warrant surgical implantation of deep brain stimulators according to standard clinical criteria."[91] Without more explicit, evidence-based criteria, clinical discrepancies could lead to inappropriate or unfair patient selection and suboptimal pDBS outcomes.

In addition to clinical factors, clinicians may take into account social support and family dynamics when determining candidacy. Indeed, our team has observed this in some of our early empirical research in this context. Some have argued that the social component is important for candidacy determinations to ensure that patients have adequate social and psychological supports throughout the long-term process of DBS.[92] While this may be true in theory, what specifically does proper social support look like and what degree does it play in DBS outcomes, if any? In other clinical contexts, such as organ transplantation, definitions of social support have been found to lack transparency and to vary across institutions.[93] In those contexts, evidence has failed to demonstrate that social support leads to different clinical outcomes. Despite this lack of evidence, this criterion is still used when determining organ recipients.[94] Ethicists have expressed concern about this, arguing that lack of evidence combined with the ambiguity and inconsistency in social support criteria creates room for bias, and potentially unnecessary or inappropriate clinician gatekeeping.[95] In other contexts, such as left ventricular assist device implants, clinicians also use the

notion of social and family support in different and inconsistent manners to determine candidacy.[96] These two examples illustrate the need to consistently define and precisely understand the role social and family support may play in pDBS. Establishing clearer pDBS candidacy criteria will be essential for ensuring clinically appropriate and fair patient selection, and ultimately avoiding the same candidacy concerns in the pDBS context.

Access and Cost Barriers:

Beyond clinical risks, it is critical for patients and families to be aware of other burdens of DBS, including potential financial costs. DBS is currently offered under an FDA Humanitarian Device Exemption.[97] A Humanitarian Device Exemption does not imply that the device is safe or effective. Applicants simply need to show that there is "probable benefit" and that it "will not expose patients to an unreasonable or significant risk."[98] Thus, health insurance providers are not legally required to cover DBS for dystonia because they can claim it is an experimental use and not medically necessary. As a result, third party payers could potentially use what some have referred to as bait-and-switch tactic when funding off-label DBS: preapproving DBS coverage, but then denying reimbursement.[99]

Uncertainties in DBS coverage are particularly concerning given the high cost of this intervention in both adults and children. On average, DBS surgery costs a total of $65,000 per patient in the US, and battery replacements cost between $10,000 and $20,000 three years post-surgery.[100] Families may face additional costs if complications arise requiring surgical revisions or device removal. Revision-associated costs are approximately $10,908 (+/− 6,469) and explantation-associated costs are approximately $12,729 (+/− 3,284).[101] The possibility of these additional costs should be taken seriously given that infection rates are twice as common in children compared to adults.[102] Moreover, insurance providers may have high deductibles or be willing to cover only a small percentage of the surgical procedure to remove DBS implants after infection, which is necessary in 86% of these cases.[103] Insurance providers may also be reluctant to cover reimplantation or request proof that the patient is responding to this experimental intervention before deciding whether they will cover reimplantation costs.

The high cost of pDBS and uncertainties in coverage therefore generate access to care concerns for most families. Moreover, the additional financial stress families experience can negatively impact patient outcomes, and clinicians may be less inclined to offer pDBS to dystonia patients even if they could benefit significantly from this intervention.[104,105] Thus, for many families, agreeing to pDBS for dystonia maybe a risky proposition, both from a clinical and financial standpoint.

Managing Expectations and Unrealistic Optimism:

Another important area of ethical concern and attention is managing expectations in pDBS cases. Families are often understandably desperate to alleviate motor impairment, and as a result, may be willing to take on a greater amount of risk regardless of the degree of symptom improvement their child may experience.[106] For example, families may exhibit something that behavioral psychologists call "commission bias," believing the harms of not trying an intervention are worse than the harms the intervention may cause, no matter

what.[107,108] Simply put, doing something for their child is better than not trying at all regardless of the risk-benefit profile. Desperation could also cause families to overemphasize potential benefits while downplaying risks of pDBS, leading to unrealistic expectations. This "unrealistic optimism" is a common phenomenon in medicine, occurring when "a person has a desire for a certain outcome and overestimates the probability of the desired outcome."[109] For example, unrealistic optimism has been observed in the setting of heart failure. A study found that 7 out of 15 heart failure patients were unrealistically optimistic about their chance of receiving a transplant, believing they were on a bridge-to-transplant despite the fact that they were on a trajectory of destination therapy.[110] This presence of unrealistic optimism even after patients were informed speaks to how powerful this bias towards benefit may be.

Unrealistic optimism is often viewed as something concerning in need of "fixing" for various reasons.[111] First, bioethicists and clinicians argue that the inaccuracy of beliefs underlying unrealistic optimism hinders informed decision-making, thus undermining patient autonomy.[112] Additionally, unrealistic optimism may lead families to be ill-prepared for the realities of pDBS, thus causing harm or suffering.[113] Their optimism could also lead them to sacrifice certain opportunities and suffer as a result of these missed opportunities. For example, a family could use a large proportion of their savings to pay for pDBS expenses. If their child does not benefit from pDBS or experiences some complication, they could feel their money was wasted and should have been used to pay for their other children's college education. Lastly, the epistemic irrationality underlying unrealistic optimism may be considered normatively unfavorable or inherently bad for families.[114]

Despite these concerns, bioethicists have also argued that unrealistic optimism may not be an entirely concerning or negative phenomenon in some situations, arguing that the many benefits of hope can extend to cases of unrealistic optimism.[115] Similar to hope, unrealistic optimism may "provide sustaining power in times of trial and tribulation, which may enhance mental or physical health outcomes."[116] Families may also be unrealistically optimistic for a temporary period of time that allows them to steadily adapt and wrap their heads around the realities of their child's disorder.[117] Identifying unrealistic optimism and when it is harmful versus beneficial to patients and families, however, is a challenging task in need of further examination in the context of pDBS.

The ethical challenges discussed above frequently arise in DBS for both adult and pediatric populations. There are numerous other ethical issues that arise in pDBS and other pediatric interventions (e.g., minors may or may not have decision-making capacity, balancing interests in a decision-making triad consisting of patient, caregiver, and clinician).[118,119] Below, we discuss ethical considerations that may be relevant to pediatric and adult DBS, but may be more challenging in the pDBS context and need to be examined and approached in ways that are distinct from adult DBS or other pediatric settings.

Identity Changes:

Presently, theoretical literature dominates discussions of identity changes related to DBS, while there are only a few empirical reports of identity changes after DBS.[120,121] However, some studies in adults have suggested that DBS can affect identity, or a person's unified and enduring self-image.[122] For example, one patient explained that they became impulsive

and frequently changed their mind to the point that their children did not recognize them.[123] In another case, a patient stated: "[DBS] has allowed me to return almost to the person I was before… It's allowed me to be what I am."[124] These 'identity changes' are highly complex and related to other kinds of changes patients could experience, such as changes in authenticity, agency, and personality.[125]

Changes in identity fall into at least four potential types. First, stimulation delivered to the brain could directly affect neurophysiological processes and resultant experience and behavior in such a way that causes some change in identity.[126] Second, a patient could incorporate the device into their self-conception, and subsequently identify with a new or different identity.[127] In particular, the presence of an external hardware influencing brain activity could cause a patient to feel as though their emotions and/or behaviors are not authentic or reflective of their true identity.[128] One woman reported this kind of identity change when she was not able to cry at a funeral, wondering whether this lack of emotion was due to her DBS device.[129] Third, a patient could experience changes in identity due to the drastic alleviation of refractory symptoms DBS may cause.[130,131] Fourth, a patient's DBS device could affect their relational identity.[132] According to relational conceptions of identity, identity formation is a dynamic activity that involves the perspectives and intentions of other people.[133] Therefore, if DBS influences how other people perceive and interact with a patient, their relational identity could become altered as a result.

Ethical considerations related to identity could be exacerbated in the pDBS setting given that childhood and particularly adolescence is considered a key period for identity formation.[134,135] Any of these general types of changes related to identity could in principle be beneficial or harmful. Determining whether a given change is beneficial or harmful would ideally be accomplished through the development of surveys or other validated measures administered to patients and caregivers, alongside clinician assessment. One empirical study reported feelings of self-estrangement in a significant number of adult patients.[136] However, this study has been criticized for its conceptual understanding of self-estrangement.[137,138] Moreover, Sanneke de Haan and colleagues found that their own patient group expressed the idea of 'becoming a different person' in conflicting manners and did not report feelings of self-estrangement.[139] Thus, due to the limited amount of empirical data examining identity changes and the lack of consensus in how patients experience these changes, we cannot definitively conclude how frequently DBS may or may not cause changes in identity and how beneficial or harmful these changes may be.[140] This is therefore an issue in need of further empirical and theoretical investigation, particularly for pediatric patients at crucial stages of development.

pDBS Unknowns:

There are important unknowns of pDBS for dystonia, including its long-term benefits and harms and its effectiveness particularly for acquired dystonias. Moreover, it must be noted that unlike adult DBS, pDBS is performed in young individuals whose brains are still growing and developing, which could result in outcomes that researchers and clinicians have not yet uncovered. For example, if electrodes are implanted in a young patient, there may be potential for the electrodes to become displaced as the child's brain and skull

develop. Additionally, gliosis, or a natural immune response to the presence of electrodes creating scar tissue, could influence stimulation impedance and manifest differently in pediatric populations compared to older, adult populations. Furthermore, DBS is generally a permanent intervention. Once the device is implanted, patients are expected to require stimulation for the remainder of their lives, yet the effects, both clinical and psychosocial, of such a lifelong commitment are unclear. The degree of uncertainty in the long-term effects of DBS therefore appear to be amplified in the pediatric DBS setting. We recognize that there is little to no empirical evidence of these unknowns, and it is thus unclear how concerning some of the pediatric-specific unknowns are. However, this greater degree of uncertainty should, at minimum, be acknowledged in addition to the other known risks of pDBS.

In order to begin addressing the ethical concerns raised above, particularly concerns of unknown risks and managing expectations, we propose two practical responses: (1) establishing robust pDBS data registries, and (2) developing a pDBS decision aid (DA).

Registries and Optimizing pDBS:

In order to optimize pDBS and minimize potential harms for children, particularly children with acquired dystonia, it is critically important for researchers and clinicians to make use of pDBS registries. Registries could accelerate the identification of effective target sites and stimulation parameters for different subtypes of dystonia.[141] Registries could also minimize the risks and opportunity costs patients face because registries would decrease the likelihood that clinicians and patients pursue DBS target sites for which there is less evidence.[142] Moreover, unlike DBS for adults, a significant challenge with pDBS for dystonia is that the vast majority of these surgeries in the United States and other countries are happening outside clinical trials.[143] This makes it even more challenging to track the number of pDBS surgeries that have taken place, the target sites and stimulation parameters used, the clinical characteristics of the patients, and measured outcomes. Thus, it is even more important to have robust clinician participation in registries for pDBS.

Currently, pediatric registries are available (e.g., pediDBS, GEPESTIM), but participation in registries is limited by factors, such as concerns about intellectual property and patient privacy.[144,145] Registries for adult DBS and pDBS also focus on primary clinical outcomes and generally do not include or request information related to non-clinical aspects of life. Quality of life data can provide valuable insight into patients' and families' lives before and after DBS to understand the broader biopsychosocial effects of pDBS.[146] Other registries for pediatric devices, such as the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS) include quality of life data and quality of life measure that different clinics can utilize.[147] Including a similar feature or requirement for pediatric DBS registries would be particularly useful for comparing quality of life data across different patient groups and clinics.[148]

Decision Aid and Shared Decision Making:

As previously mentioned, there is some degree of uncertainty regarding the effectiveness, long-term effects, optimal targets and parameters, and unknown risks of pDBS for dystonia

(particularly acquired dystonia). In addition to these clinical complexities, a third party (caregiver) is legally authorized to provide consent for pDBS surgery on behalf of a vulnerable population (children) who may or may not have decision-making capacity (children ~12 and older often have sufficient decision-making capacity although not legally authorized to consent in this context).[149,150] This pDBS decision-making triad (pediatric patient-caregivers-clinicians) must balance additional values and potentially competing interests than an adult patient-clinician dyad. Moreover, pDBS is potentially a lifelong commitment that requires patients to continue stimulation for prolonged symptom management. As a result, a parent's decision on whether to pursue pDBS has a domino effect on subsequent choices the child may or may not be able to make, thus significantly affecting their future and their rights to it.[151]

Together, these various factors make decisions about pediatric DBS highly complex for clinicians and even more complex for patients and families. However, there are currently no decision aids (DAs) or tools for optimizing informed and shared decision-making in the pDBS setting. DAs for different pDBS indications could help by: 1) providing facts about the health condition, treatment alternatives, and the qualities of these alternatives; 2) assisting decision makers (e.g. caregivers in the pDBS context) to identify their values (e.g., what matters to them, what they do not feel comfortable doing) and; 3) helping decision makers to communicate these values to others (e.g., clinicians, family members).[152,153]

Conclusion

Interest and investment in DBS for pediatric disorders has quickly expanded, especially for dystonia. However, the lack of clinical trials and neuroethics challenges beg the question of whether offering DBS for children with refractory dystonia is ethically justified. In answering this question, numerous clinical complexities surface. First, dystonia can have different causes and symptoms manifest in various ways. pDBS outcomes vary significantly across different etiologies of dystonia. Other factors, including the age of onset and the development of musculoskeletal deformities, can also influence the degree to which children can benefit from pDBS. Given current risk-benefit data, we conclude that offering pDBS is ethically justified for patients with some etiologies of dystonia (inherited dystonia *without* degeneration or structural lesions and idopathic dystonia), but the benefits do not obviously outweigh the potential risks for other etiologies of dystonia (inherited dystonia *with* degeneration or structural lesions and acquired dystonia).

However, in addition to clinical analysis of risks and benefits, a number of ethical concerns must be addressed from an ethics and policy standpoint to provide a more satisfying answer to the question of whether it is ethically justified to offer pDBS for dystonia. We propose two strategies to better understand and address these ethical and policy considerations as pDBS continues to expand. First, researchers and clinicians must make use of DBS registries to more effectively optimize pDBS and minimize potential harms for children. Research and registries should collect not only primary clinical outcomes data but also data on non-clinical factors that can impact pDBS stakeholders (e.g., whether pDBS was covered by insurance, what was the impact of pDBS on quality of life). Second, a decision aid is critically important to help the pediatric patient-caregiver-clinician triad navigate this highly

complex and consequential decision. Together, data registries and a DA can help families and patients, such as Ryan, gain the clinical and psychosocial benefits of pDBS while minimizing its clinical risks and potential ethical challenges.

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